Driving CARs in solid tumors: the promise and challenges

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THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

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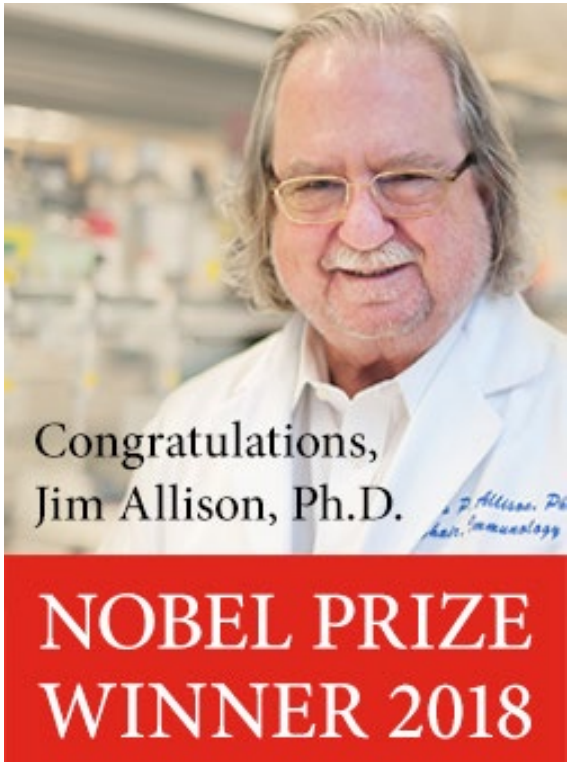
Immunotherapy changing cancer therapy landscape

http://www.sciencemag.org

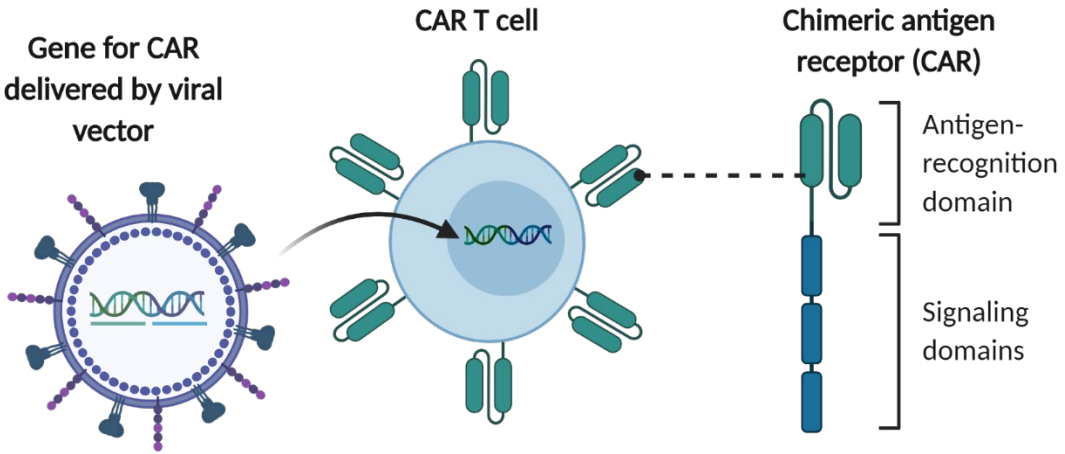


Outline

- Immunotherapy changing treatment landscape, particularly in solid tumors
- Chimeric antigen receptor (CAR) T cell therapy one form of many available immune effector cell (IEC) therapies
- Several FDA approved CARs in hematologic malignancies
- CARs in solid tumor greater ramification greater numbers patients
- Logistical challenges
  - Complex therapy requires multi-disciplinary care model
  - Regulatory aspect
  - Data reporting
  - Cost

Chimeric antigen receptors

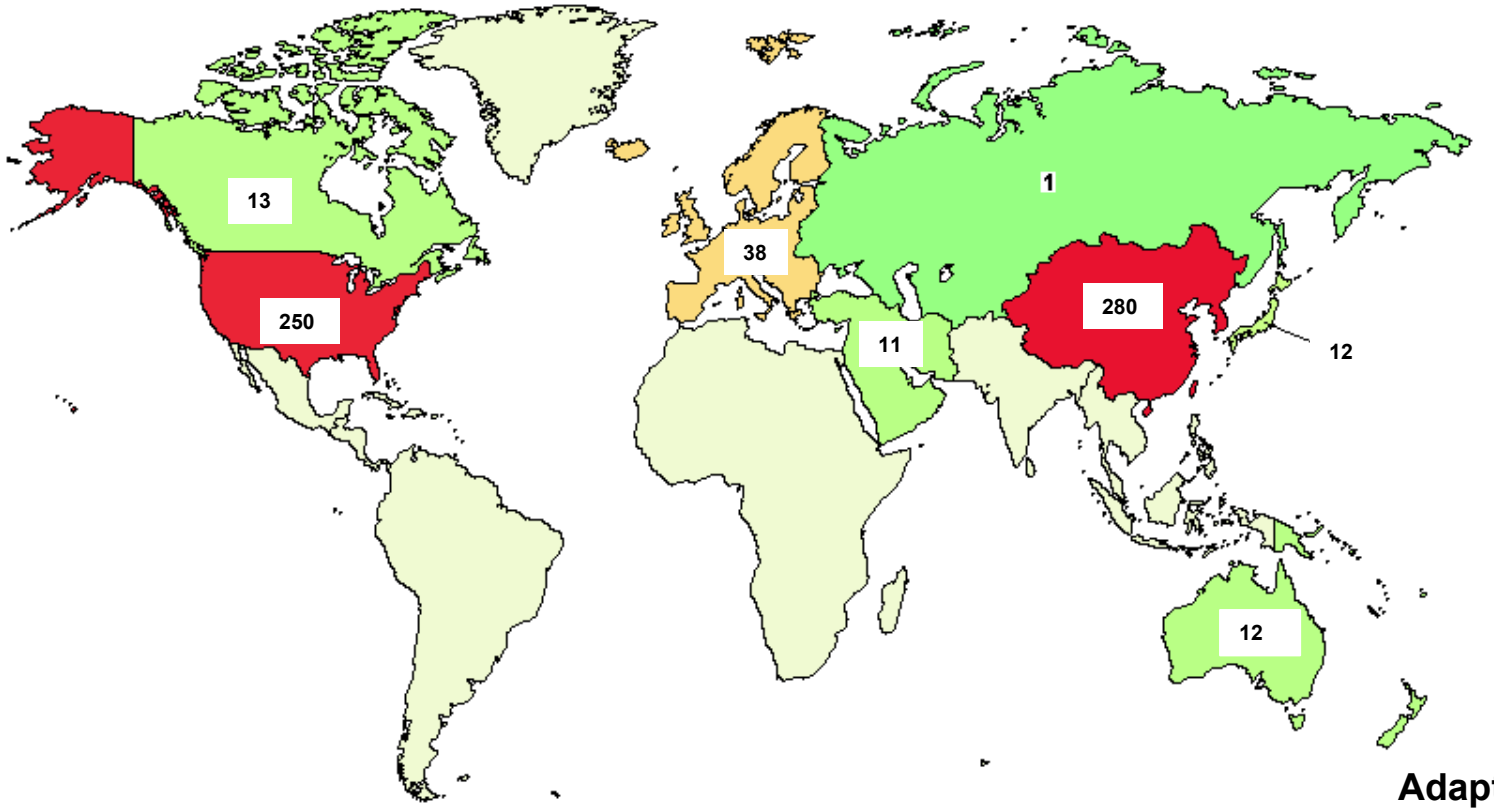
- Overcome immune tolerance
- Targets surface molecules in native conformation
- Independent of antigen presenting cell and MHC complex



FDA-approved CAR T therapies

Drug	Target/co-stim domain	Indication	Dose	Response	Grade 3-4 Toxicity
Axicabtagene ciloleucel (FDA 2017)	CD19/CD28ζ	R/R DLBCL, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma	2 x 10^6 CAR-positive, viable T cells per kg bodyweight (up to 2x10^8)	ORR: 83% CRR: 58% 2-yr OS: 50%	CRS: 11% ICANS: 32%
Tisagenlec-leucel (FDA 2017)	CD19/4-1BBζ	Patients ≤25 yr with R/R B-ALL	0.2-0.5x10^6 CART/ kg if <50kg; 0.1-2.5x10^8 CAR T/kg if >50 kg	ORR: 82% CRR: 62% 2-yr OS: 66%	CRS: 46% ICANS: 13%
Tisagenlec-leucel (FDA 2018)	CD19/4-1BBζ	R/R DLBCL, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma	0.6-6.0 x 10^8 CAR T cells	ORR: 52% CRR: 40% 1-yr OS: 49%	CRS: 22% ICANS: 12%
Brexucab-tagene autoleucel (FDA 2020)	CD19/CD28ζ	R/R mantle cell lymphoma	2 x 10^6 CAR T/kg (up to 2x10^8)	ORR: 86% CRR: 57% 1 yr OS: 86%	CRS: 18% ICANS: 46%
Idecabtagene vicleucel (FDA 2021)	BCMA/4-1BBζ	R/R multiple myeloma	3- 4.6 x 108 CAR-positive T cells	ORR: 73% CRR 33%	CRS: 9% ICANS: 4%

Rush Hour



Total Trials by date:

605 -- 04/2021
370 – 04/2019
317 – 09/2018
220 – 08/2017
123 – 05/2016
77 – 09/2015
<5 – 2010

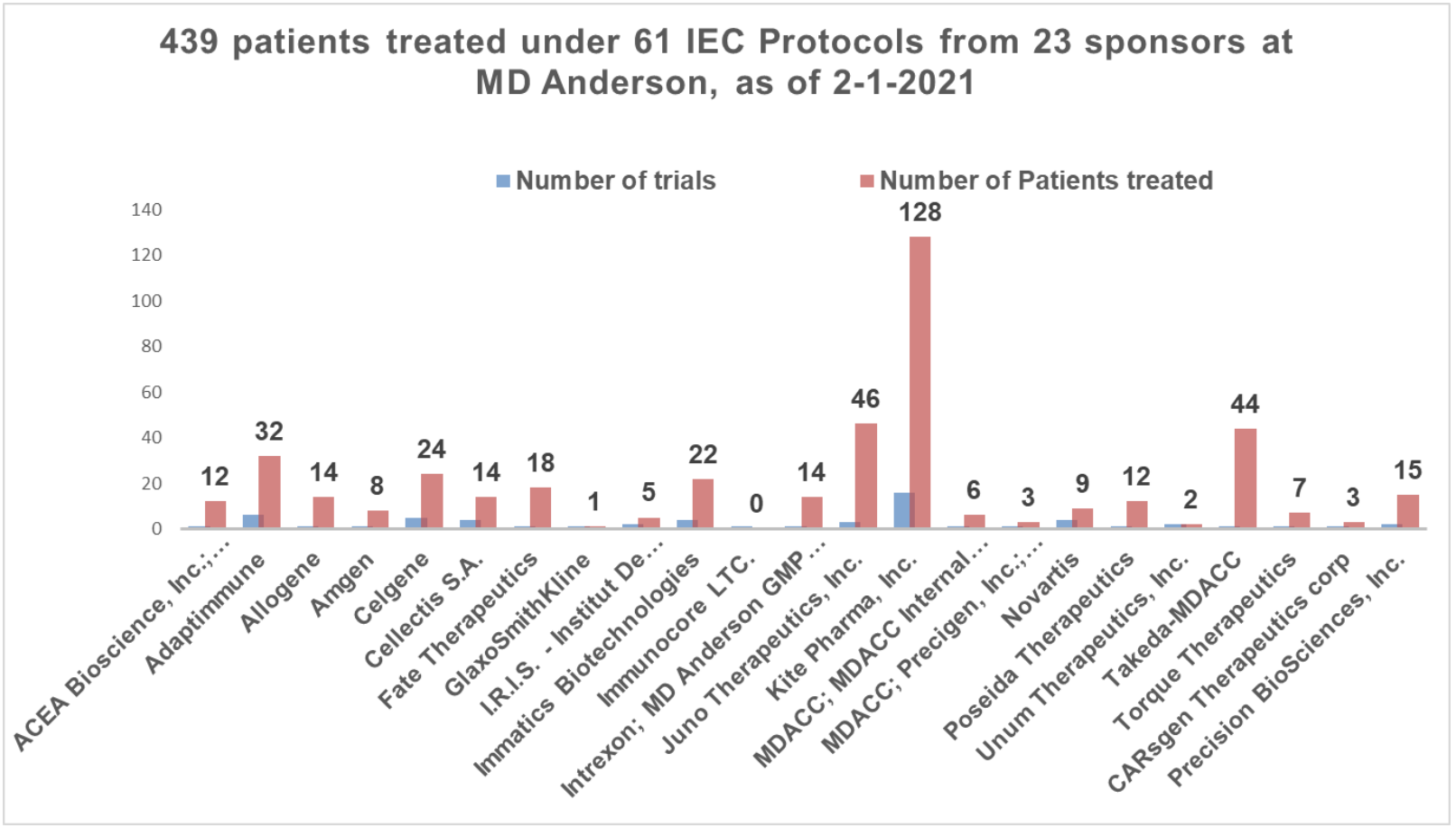
Map as of 04/2021

Search term: "chimeric antigen receptor"

ClinicalTrials.gov

Adapted from Dr. Frigault

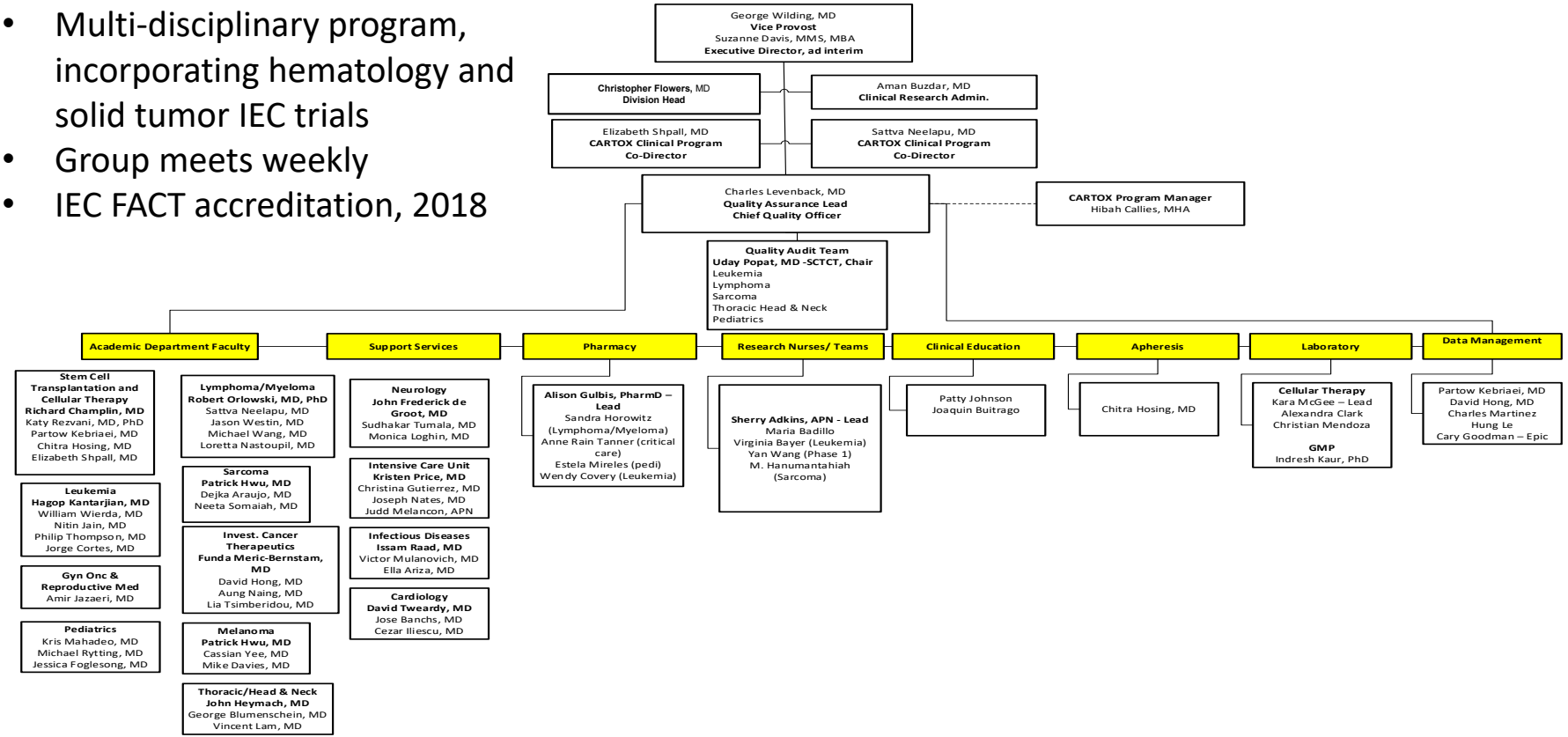
IEC studies, sponsors, and patients treated



IEC therapy targets of active studies at MDACC

MDACC CARTOX Program, est. March 2016

- Multi-disciplinary program, incorporating hematology and solid tumor IEC trials
- Group meets weekly
- IEC FACT accreditation, 2018



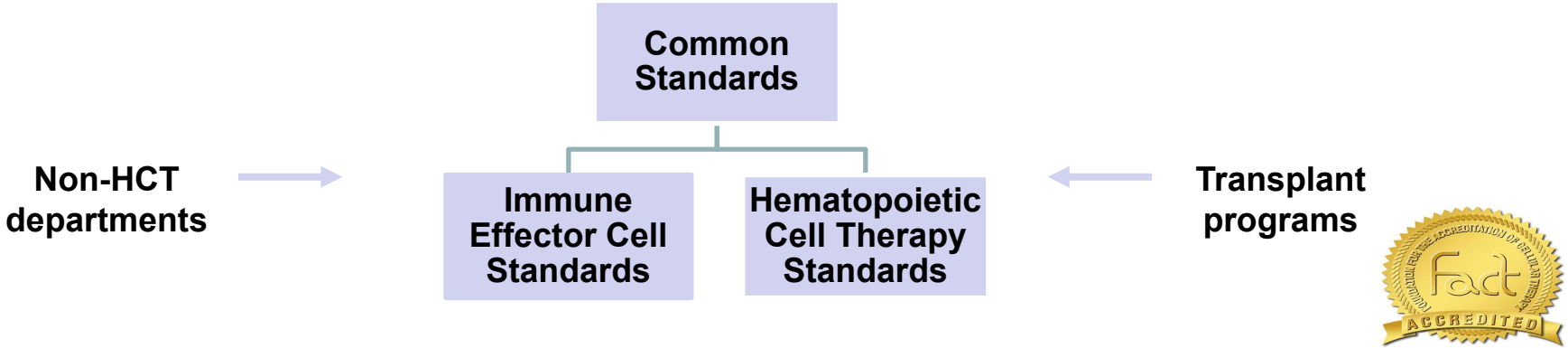
Care of solid tumor patients receiving IEC therapies at MDACC

- Apheresis collection for product manufacture in SCT
- In-patient care on designated units by SCT in-patient team
- Toxicity grading and management based on consensus guidelines developed for hematologic malignancies[1]
- Out-patient care jointly with solid tumor and SCT service through day 30
- Currently, data collection protocol specific and limited to protocol study team

1. Lee et al. Biol Blood Marrow Transplant. 2019 Apr;25(4):625-638

FACT standards for IEC

- IEC: Broadly defined as “cells that have differentiated into a form capable of modulating or effecting a specific immune response”
- Foundation for Accreditation of Cellular Therapy (FACT) pubished IEC standards in January 2017 using HCT standards format
- Designed to be flexible to accommodate various models of patient care and use of cellular therapy products
- Expanding accreditation to non-HCT programs



Importance of IEC therapy accreditation

FACT-accredited transplant programs

- Participation in immune effector cell trials
- Desire to apply FACT requirements to these new services
- **80/20 Initiative**

Drug manufacturers

- Investment in controlled, safe clinical trials
- Ensure continued proper handling and use of products after licensure

Patient Safety, Outcomes, and Access

Regulators

- Responsibility for approving only safe and effective products for licensure
- Interest in field's ability to handle toxicities

Payers

- Anticipation of drug licensure → requests for reimbursement
- Expectation of good outcomes for covered services

IEC clinical outcome reporting

- How will the results with the SOC and protocol IEC products be reported to allow population wide analysis and maximal dissemination of results?

- **CIBMTR** awarded the Cellular Immunotherapy Data Resource (**CIDR**), led by Dr. Marcelo Pasquini
  - Database contract as part of NCI moonshot Initiative
  - Contracting with pharmaceutical companies to manage long-term follow-up data

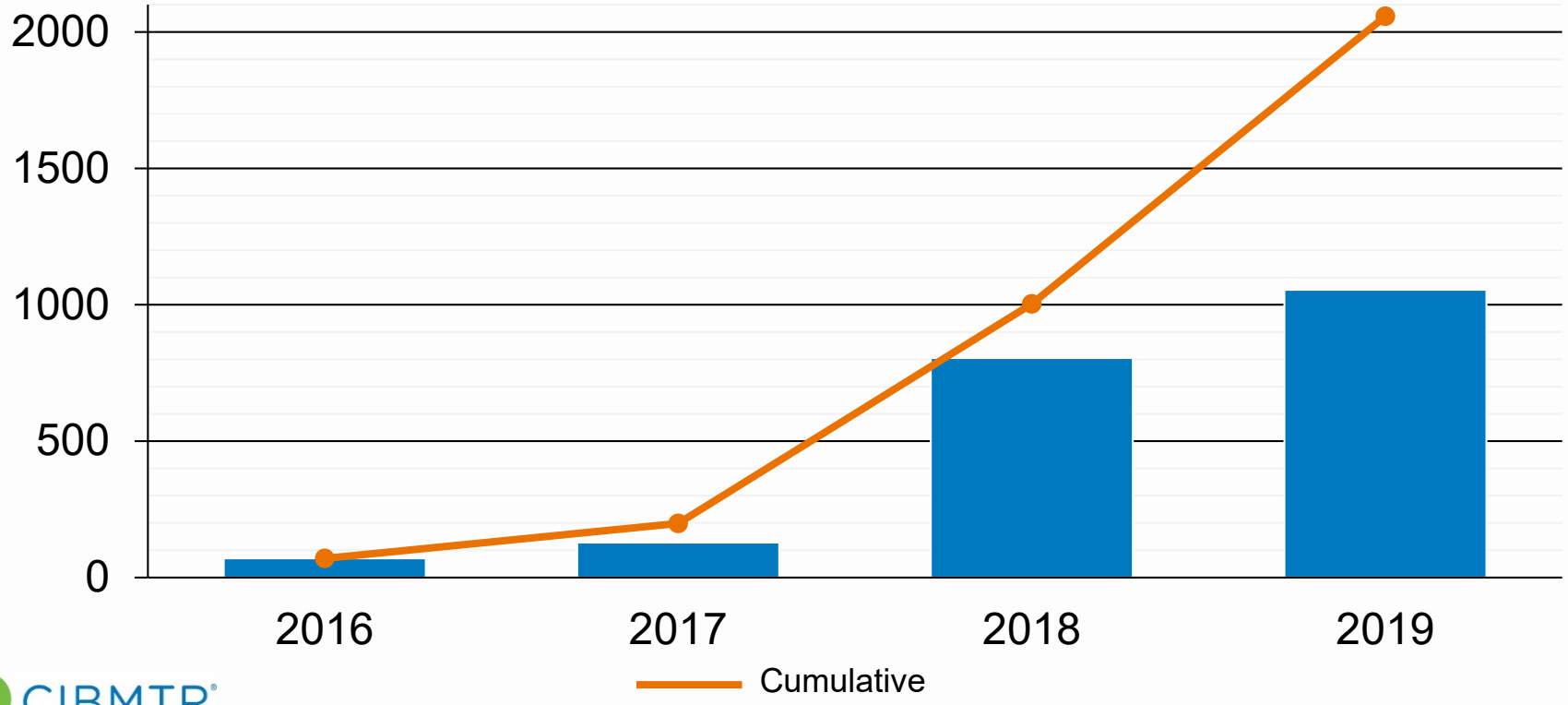
Overall goals of the CIDR

- To provide the academic community, as well as relevant pharmaceutical partners, with an infrastructure for collection of high quality data.
  - Demographics, tumor characteristics, course of cancer treatment, cellular product manufacturing details, adverse events and outcomes
  - Patients treated in either clinical trials or with FDA-approved agents
- Scope:
  - Cellular therapies for cancer (**solid tumors**, heme malignancies, viral infection–associated malignancies)
  - T-cell based adoptive therapy (CTLs, TILs), genetically modified cells (CAR, modified TCR, other gene editing approaches)
  - Data on cellular therapy manufacturing

CIDR
CELLULAR IMMUNOTHERAPY DATA RESOURCE

Annual Number of Recipients of CAR T cells: 2016-2019 (2,058 patients and 2,217 infusions)

CIDR
CELLULAR IMMUNOTHERAPY DATA RESOURCE



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Data Incomplete for 2019

CAR T Cell Indications: 2016-2019 (N=2,058)

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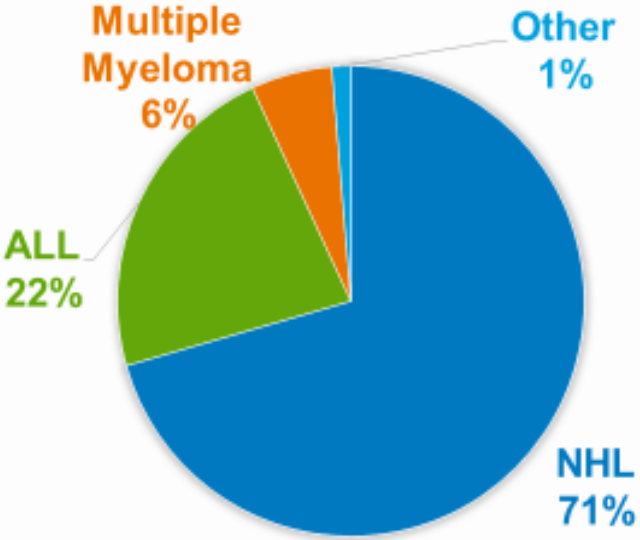
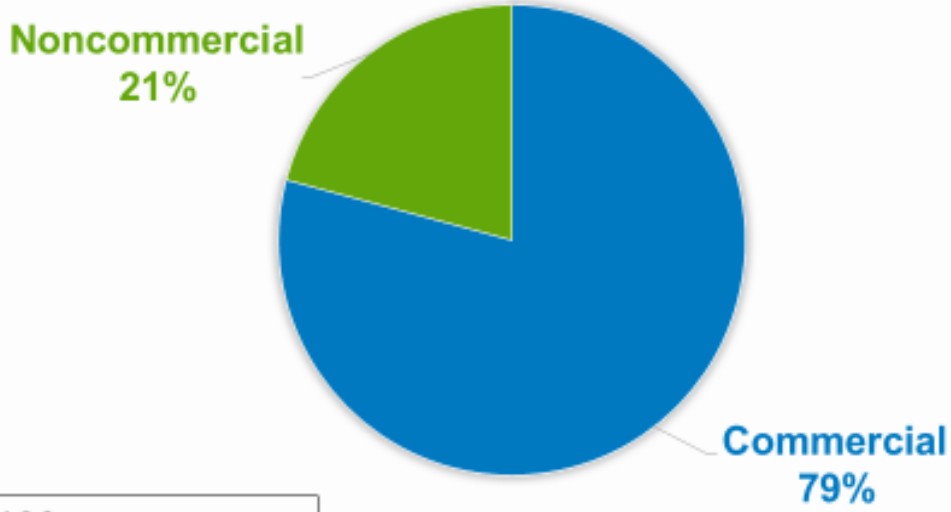
CELLULAR IMMUNOTHERAPY DATA RESOURCE





Centers: 123
Median age: 57 y (<1-91)y
Prior HCT: 37%

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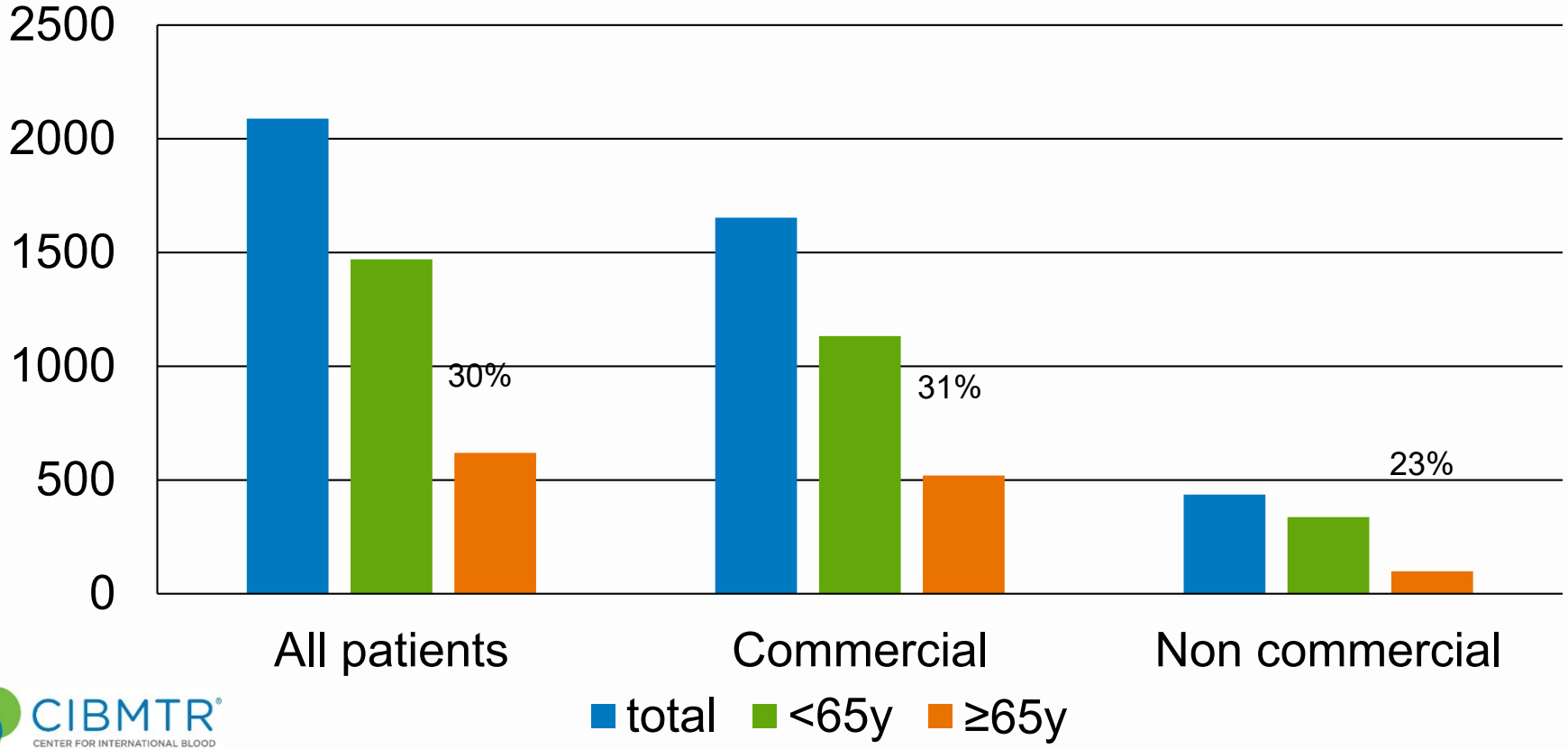
Distribution of CAR T-cell Recipients by Age and Commercial Product (N=2,053)

CIDR
CELLULAR IMMUNOTHERAPY DATA RESOURCE



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Data management in solid tumors

- CIDR organized a task force of experts May – September 2020 to discuss the landscape and future of cellular therapy in the treatment of solid tumor patients, and to inform the role of CIDR and CIBMTR data collection for these patients.

Targets under investigation

CIDR
CELLULAR IMMUNOTHERAPY DATA RESOURCE

Target	Target	Target	Target	Target	Target	Target	Target	Target	Target	Target	Target	Target	Target	Target	Target	Tumor
CD133	CEA				EpCAM			HER2	MSLN		MUC1	CD70				Breast cancer
																Cervical
CD133								HER2								Glioma
CD133	CEA		EGFR		EpCAM			HER2			MUC1					Coloreectal
																Fibrosarcoma
	CEA	Claudin 18.2			EpCAM			HER2			MUC1					Gastric
								HER2								Germ cell tumor
			EGFR	EphA2							MUC1					Head/neck
																Hemangiosarcoma
					EpCAM		GPC3			MG7						Hepatobilliary
	CEA		EGFR				GPC3	HER2	MSLN							Lung
						GD2										Neuroblastoma
CD133								HER2	MSLN							Ovarian (epithelial)
CD133	CEA	Claudin 18.2			EpCAM		GPC3	HER2	MSLN		MUC1	CD70				Pancreatic
													PSMA			Prostate
												CD70				Renal cell
															NY-ESO	Sarcoma
									MSLN							Uterine
														ICAM-1		Thyroid

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Taskforce findings

- Current therapy landscape
  - Diverse disease histology
  - Varied IEC products with different targets – single vs. multiple
  - Varied kinetics of response and toxicity profile
  - Care of patients may be shared across departments
- Challenges identified included
  - How to classify, histology vs. target
  - Extensive prior therapies
- Potential uses
  - Gathering long-term follow-up data as required by FDA
  - Data for rare tumor types

Conclusion

- IEC therapy is revolutionizing care in solid tumor patients
- CAR T therapy in solid tumors in infancy
- Lessons learned from hematology space can inform approach in solid tumor
  - Multidisciplinary care, IEC accreditation, data reporting instrumental in optimal delivery and understanding of therapy

THANK YOU

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